REVIEW

Perspectives on Comparing Risks of Environmental Carcinogens[1]

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In 1987, investigators (Ames et al.) concluded that the risks of man-made industrial carcinogens and pesticides (outside of the workplace) are trivial compared with the risks of naturally occurring carcinogens found mostly in the diet. They used a ranking system based on human exposure and rodent potency (HERP) data to arrive at this conclusion. As a result, they recommend that regulatory agencies, such as the Environmental Protection Agency and the Food and Drug Administration, base their priorities in this area on their HERP system. We analyzed the assumptions and data set upon which the HERPs were based, concluding that such a simplified approach to set public health policy is inappropriate given the underlying uncertainties. However, we note that when comparisons are consistently based on estimates of average daily exposure to common carcinogens, the HERP scores of many man-made pollutants are comparable to those of naturally occurring carcinogens in the diet. [J Natl Cancer Inst 1988;80:1282-1293]

Background

The majority (an estimated 60%-90%) of human cancer is considered to be attributable to environmental factors, broadly defined to include cigarette smoking, industrial pollutants, radiation, diet, and perhaps other life-style factors and viruses (*1*). Thus, in theory most cancer is preventable through the identification and control of causative factors, including exposure to carcinogens. For decades, policymakers concerned with the assessment and regulation of environmental carcinogens have searched for a systematic way to set priorities among the many candidates. This paper critically evaluates the most recent proposal for such a ranking scheme (*2*).

Identification of specific etiologic factors and estimation of their relative importance constitute a formidable task. Few cancers are attributable to single factors or exposures; rather, complex interactions between environmental and host factors are generally involved (*3-5*). Moreover, because of the limitations of epidemiology (*6*), only rarely are human data available that directly link an environmental agent to human cancer. For example, epidemiological studies strongly suggest, although they do not conclusively establish, an association between organic chemical carcinogens in drinking water (such as chloroform) and cancers at several sites, including the rectum, colon, and bladder (*7-11*). Certain dietary and nutritional factors (such as dietary fat and fiber) have been implicated in cancer of the breast, colon, rectum, and stomach (*12,13*), but here too a direct causal association has not been established for specific dietary constituents. In addition to active cigarette smoking and a significant number of pollutants in the workplace, established tc human lung carcinogens (*14*), there is growing evidence t passive smoking (*15*) and pollutants in the ambient air (*16,17*) contribute significantly to lung cancer mortality. However, because of cost and feasibility constraints and the difficulty in identifying an appropriate study population, the vast majority of animal carcinogens, both naturally occurring and man-made, have neither been the subject of epidemiological investigation nor are they likely to be (*18*). Thus, for practical purposes, as a matter of long-standing policy, regulatory agencies accept the use of positive animal data as predictive of carcinogenic hazard in human beings (*19*). The alternative, awaiting positive evidence of carcinogenicity in humans,

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traditionally has been rejected as morally and socially unacceptable.

A major limitation of epidemiology (and risk assessment) is that reliable data on human exposure to specific chemicals are frequently lacking. Therefore, by necessity, most epidemiological studies have relied on crude or indirect measures of exposure. A significant number of carcinogens have been detected in drinking water, ambient air, and the food supply; however, reliable monitoring data exist for only a small fraction of these chemicals. For example, while dozens of pesticides and industrial chemical carcinogens have been measured routinely in surface water, groundwater, and drinking water, they represent only a small percentage of chemical pollutants present (*10,20–23*). Over 700 organic chemicals have been found to be present in the U.S. drinking water supply, including 40 known or suspected carcinogens (*24*). Numerous carcinogenic air pollutants (trace metals, polycyclic aromatic hydrocarbons, and volatile organic chemicals) have been detected in ambient air; again, there are little or no reliable monitoring data on the majority of airborne carcinogens (*25*). Similarly, many carcinogenic pesticide residues have been identified in the food supply, but reliable exposure data are lacking for most (*26*). Testifying to the pervasiveness of environmental contamination are studies showing significant concentrations of synthetic organic chemicals in the blood, urine, and/or adipose tissue of the U.S. population. These include 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane (DDT), dieldrin, heptachlor epoxide, polychlorinated biphenyls (PCBs), and dioxin (*27,28*). Again, data are far from comprehensive; however, they do show a decline in the concentrations of DDT and PCBs as a result of regulation.

Despite their limitations, available exposure and epidemiologic data have served as the basis for a number of widely varying estimates of the proportion of human cancer in the U.S. population that can be attributed to life-style, occupational exposures, or other environmental pollution. These exercises have generated significant debate, as much over the underlying assumptions as the data used to generate them (*17,29–35*). Unfortunately, various such estimates (ranging, for example, from 4% to >20% for occupational exposures) have been cited as a basis for setting priorities for public health protection. This approach ignores both the underlying uncertainties, the relative preventability of various risk factors (*36*), and the disproportionate impact on some segments of the population. For example, once recognized, most chemical pollutant hazards can be reduced or eliminated by practical means. Moreover, the involuntary nature of these exposures necessitates control at the source, in contrast to exposures related to life-style (e.g., diet and smoking), which can be addressed more effectively through public education regarding personal behavioral choices. Another inherent problem with the approach of estimates is that it obscures the much higher risks to certain subpopulations. For example, if the contribution of occupational carcinogens to all cancer deaths in the United States were as low as 3%, for male industrial workers as a group, workplace carcinogens would account for at least 25% of all identified causes of cancer (*33*).

Another tool that has been used increasingly by regulatory agencies to set priorities and even to determine acceptable levels of exposure to individual environmental contaminants has been quantitative risk assessment. Here, also, the lack of good information on human exposure as well as the usual paucity of epidemiological data are compounded by uncertainties regarding the proper way to extrapolate from high to low dose and from experimental animals to humans (*37*). To offset these uncertainties, the four major U.S. regulatory agencies, including the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), the Consumer Product Safety Commission, and the Food and Drug Administration (FDA), have traditionally preferred conservative models that incorporate an assumption of low-dose linearity, regardless of the presumed mechanism of action of the chemical carcinogen (*19*). However, in certain instances, these conservative models may underestimate cancer risk. For example, the widely accepted linearized multistage model (*38*), considered to be one of the most conservative of the biologically plausible risk-assessment models, works on the assumption that the exposed population is of uniform susceptibility and that interactions do not occur between chemical exposures and other risk factors. Yet significant intraindividual variability has been demonstrated for human metabolism and binding of drugs and carcinogens (*39–45*) as well as for repair of DNA damage (*46*). Moreover, a number of epidemiological studies have demonstrated synergism between chemical exposures and host factors, such as cigarette smoking and air pollutants in the workplace and urban air (*47,48*). To further complicate the situation, although nonlinear (both superlinear and sublinear) dose-response relationships have been observed experimentally and epidemiologically, the available data do not allow low-dose linearity to be ruled out in any of these cases (*49*). Given these uncertainties, it is reassuring that, in a number of cases, risks observed in humans have been consistent with those calculated from high-dose animal experiments with the use of models that incorporated linearity at low dose. These include benzene, ethylene dibromide (EDB), gasoline, asbestos, and ethylene oxide (*50–56*). Therefore, there is general agreement that the use of quantitative risk assessment, performed with appropriate and consistent assumptions and models, affords the possibility of comparing risks for the purpose of setting priorities among selected candidates for regulation. However, most scientists do not view quantitative risk assessment as capable of providing precise estimates of human risk from individual chemicals; general sources of chemical exposures are considered even less likely candidates for risk estimation by this method.

Human Exposure/Rodent Potency (HERP) Index

Most recently, researchers at the University of California at Berkeley and Lawrence Berkeley Laboratory have suggested still another approach to priority setting (*2*). They have calculated a possible hazard index for selected carcinogens by expressing the human exposure (in milligrams/kilogram) as a percentage of the rodent TD_{50} dose

(also in milligrams/kilogram).[4] They have compared the resultant HERP indices for four pollutants found in drinking water and indoor air, three man-made pesticides and other residues, 10 natural pesticides and dietary toxins, two food additives, five drugs, and two occupational exposures (*see* table 1). The authors conclude that man-made environmental pollutants, such as pesticide residues and contaminants in drinking water, are "likely to be of minimal carcinogenic hazard" relative to the background of natural carcinogens (found largely in the diet). They recommend that regulatory agencies that traditionally have emphasized control of exposures to man-made or industrial carcinogens (in addition to those in the occupational setting) revise their priorities.

The authors acknowledge several major limitations of the HERP system, such as the possibility of interspecies (rodent and human) variation in susceptibility to carcinogens and quantitative uncertainties regarding the general shape of the dose-response curve, including the possibility of synergistic effects and thresholds for nongenotoxic carcinogens, such as promoters (*see* discussion below). They caution that it would be a mistake to use the HERP index as a direct estimate of human hazard, but they conclude that the scale provides "a way of setting priorities for concern."

Although this is an innovative approach, it suffers from several inherent flaws. First, as we will show in table 2, the results are influenced strongly by the selection of chemicals and whether one classifies them as "man-made" or "natural." The rationale for selection of the individual compounds in table 1 was not provided by the authors, but presumably it was dictated by the nature and availability of both exposure and rodent potency data. As mentioned, the rodent potency data base is not comprehensive. For example, it omits a number of carcinogenic pesticides including alachlor, which is of current concern as a food contaminant (*26*) and has been found in water supply wells at significant concentrations (*61*). Certainly, the four selected drinking water and air pollutants and the pesticides listed cannot represent the large number of industrial chemicals and pesticides that have been detected frequently in the U.S. drinking water, air, and food supply and that also have evidence of carcinogenicity in humans and/or laboratory animals (*62,63*).

Moreover, although we are aware that there are many potential dietary hazards, the majority of which also are not well characterized (*2,64*), the 10 natural dietary carcinogens in table 1 include a number of exotic foods to which the U.S. general population has limited exposure (sake, comfrey

Table 1. Possible carcinogenic hazards, as ranked by Ames et al. (2)*

Possible hazard (HERP %)	Carcinogenic exposure
	Man-made chemicals in foods and beverages
0.0002	PCBs.† U.S. average daily dietary intake
0.0003	DDE/DDT.† average daily dietary intake
0.0004	EDB, average daily dietary intake from grains/grain products
0.0002	Furylfuramide in 2-fluorenamine, daily dietary intake before banning
0.06	Saccharin† in 12-oz diet cola
	Natural carcinogens in foods and beverages
0.003	DMN in 100 g of cooked bacon
0.006	DEN in 100 g of cooked bacon
0.003	Urethane in 250 mL of sake
0.03	Symphytine in 1 cup of comfrey herb tea
0.03	Aflatoxin in 1 peanut butter sandwich
0.06	DEN in dried squid, broiled in gas oven
0.07	Allyl isothiocyanate in 5 g of brown mustard
0.1	Estragole in 1 g of dried basil leaf
0.1	Hydrazines in 1 raw mushroom
0.2	Safrole in natural root beer, before ban
0.008	DMN in 12-oz beer, before 1979
2.8	Ethyl alcohol† in 12-oz beer
4.7	Ethyl alcohol† in 250 mL of wine
6.2	Comfrey root in comfrey-pepsin tablets, 9 daily
1.3	Symphytine in comfrey-pepsin tablets, 9 daily
	Indoor air pollutants
0.6	Formaldehyde in conventional home air, 14 hr/day
0.004	Benzene in conventional home air, 14 hr/day
2.1	Formaldehyde in mobile home air, 14 hr/day
	Water pollutants
0.001	Chloroform† in tap water, 1 L U.S. average
0.004	Tetrachloroethylene† in well water, 1 L, highly contaminated
0.0002	Chloroform† in well water, 1 L, contaminated
0.0003	Tetrachloroethylene† in well water, 1 L, contaminated
0.008	Chloroform† in average swimming pool, 1 hr
	Drugs
0.3	Phenacetin, average dose
5.6	Metronidazole, therapeutic dose
14	Isoniazid, prophylactic dose
16	Phenobarbital, 1 sleeping pill
17	Clofibrate,† average daily dose
	Occupational exposure
5.8	Formaldehyde, worker's average daily exposure
140	EDB, worker's daily intake, high exposure

*DMN = *N*-nitrosodimethylamine, and DEN = *N*-nitrosodiethylamine.
†Carcinogens characterized by Ames et al. as nongenotoxic and likely to have thresholds.

[4]Here the TD_{50} is the average daily dose rate to halve the percent of tumor-free animals by the end of a standard lifetime (*57*). The average TD_{50} is calculated by taking the harmonic mean of the TD_{50}s of the positive tests in the most sensitive species. From each test, the target site with the lowest TD_{50} value was used. In general, the harmonic mean and the lowest TD_{50} differ by a factor of ~2 (*58*). The source of TD_{50} values is the Carcinogenic Potency Data Base (CPDB) (*57-60*). The data base is a compilation of results from >3,500 experiments on 975 chemicals. It includes results from the Carcinogenesis Bioassay Program of the National Cancer Institute/National Toxicology Program (through May of 1986) as well as studies published in the literature (through December of 1984). The data base is restricted to tests that meet very stringent methodologic criteria. Thus certain human carcinogens (such as asbestos and tobacco smoke) are excluded; seven chemicals regarded by the International Agency for Research on Cancer (IARC) as having sufficient evidence of carcinogenicity in animals (cadmium chloride, cadmium sulfate, epichlorohydrin, glycidaldehyde, isosafrole, mestranole, and 2-nitropropane) are recorded in the CPDB as having only negative tests. The CPDB is a useful tool, but its limitations should be kept in mind.

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herb tea, dried squid, brown mustard, and comfrey-pepsin tablets). Therefore, comparisons between drinking 1 L of water containing average concentrations of chloroform and eating a daily serving of dried squid ignore the fact that the average American adult ingests an estimated 2 L or more of water a day (*65*)[5] and rarely, if ever, eats dried squid.

An additional problem is that several "natural pesticides and dietary toxins" in table 1 are misclassified in that they can result from harvesting, manufacturing, or cooking processes and therefore cannot be considered to be strictly natural. For example, aflatoxin in nuts and grains is partially attributable to improper harvesting and storage procedures, whereas, as the authors acknowledge, nitrosamines are formed in cured meats through the reaction of secondary amines with nitrites added as preservatives. Carcinogenic nitropyrenes and nitrosamines occur in browned or burned meats as a result of cooking with gas flames that generate NO_2 (*2*).

Moreover, a number of natural substances or food additives in table 1 have been banned (safrole in natural root beer and AF-2, a Japanese food additive never used in the United States) (*67*), so that there is no current exposure to the U.S. population. Several of the environmental pollutants have been regulated (chloroform, PCBs, and EDB) or even banned (DDT), so that postregulatory exposures (and HERPs) are predictably low, testifying to the effectiveness of regulation.

A second major limitation of the approach of Ames et al. derives from the fact that, as can be seen in table 1, varying exposure indices were used. For waterborne and airborne contaminants, daily exposure was calculated; for pesticides and other residues in food, daily average dietary intake was provided; for "natural" carcinogens in food, one serving was assumed to occur daily; for food additives and drugs, several different measures were used.

To illustrate the effect of chemical selection and of assumptions regarding levels of exposure, we have constructed table 2; it includes all of the chemicals/exposures in table 1, except for those dietary constituents not widely consumed in the United States and those that have been banned and have no current U.S. exposure. We have also omitted drugs because exposure is generally of short duration; drugs are a special case because they are prescribed when benefits are thought to outweigh risks to the individual. Finally, we have included in table 2 several chemicals or sources of exposure that are encountered commonly by the U.S. population and for which rodent potency (*58-60*) and exposure data are available. Unfortunately, in several cases environmental chemicals of concern were in the rodent potency data base, but we could not find reliable exposure data for specific media. This was true for dioxin or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). However, according to the EPA, a crude estimate of total daily intake of dioxin by sizeable segments of industrialized populations is 1 pg/kg (*28*), which corresponds to a HERP of 0.004.

To avoid the problems of inconsistent exposure indices, we have adopted in table 2 the standard approach of uniformly providing average daily dose to the U.S. adult. We recognize both the uncertainties in available exposure data (*143*) and the fact that the average estimates mask wide interindividual variation in exposure depending on geographical, cultural, economic, social, and host factors. For example, a child's exposure to pollutants in drinking water is proportionally greater than exposure of the adult, because children ingest an estimated 1 L of water per 10 kg of body weight compared with 2 L or more per 70 kg of body weight for the adult (*65*). Children may also consume more of a contaminated food than adults. In the case of the pesticide daminozide, the daily dose to the U.S. child (1-6 yr) from consumption of apples, apple juice, and peanut butter is from fivefold to 15-fold higher than the daily dose to the U.S. adult (*70,71*.)

Thus, there are obvious drawbacks to using each of the possible exposure indices (average, worst case, general population, or sensitive subpopulation). However, it is imperative in making comparisons that the same measure of exposure be used consistently. This is demonstrated by table 3 in which we compared HERPs from tables 1 and 2 for the same compound.

As mentioned above, postregulatory exposures (and HERPs) for environmental carcinogens such as DDT/DDE (1,1-dichloro-2,2'-bis(*p*-chlorophenyl)ethylene) are low. Therefore, in a number of cases we have included preregulatory and postregulatory values for purposes of comparison.

Unfortunately, any listing of chemicals such as in tables 1-3 cannot convey the reality of cumulative exposures to different carcinogens in the same medium. Also, it does not reflect the possibility of interactions among them or the need to consider exposures to the same chemical via several different media. For example, the individual has exposure to synthetic volatile organic compounds in the drinking water from ingestion, from dermal absorption while bathing or showering, and from inhalation of the volatilized compound (*144*). Humans may be exposed concurrently to the same carcinogenic substance via a number of different sources and media. For example, in considering the risk of EDB in grain, the New York Department of Health reasonably chose to sum the potential risks of the pesticide in food, ambient air (from use of unleaded gas), and drinking water (*145*).

Finally, an important distinction not conveyed by either table 1 or table 2 is that between voluntary and involuntary exposure. As discussed in the introduction, individuals are capable of voluntarily reducing exposure to substances in diet and cigarette smoke that have been identified as carcinogenic hazards. By contrast, individuals cannot feasibly control their exposure to air, water, and workplace pollution.

In tables 2 and 3, we have attempted to demonstrate the susceptibility of the HERP system (or any such simplified approach) to the effects of selection of both chemicals and exposure estimates. As is clear from table 3, the differences between tables 1 and 2 are largely because of these two factors. In contrast to that of Ames et al. (*2*), our approach, incorporating a representative set of exposures to the U.S.

[5]In fact, the results of a recent water consumption survey show that for 5% of adults 20-64 yr old, the average daily consumption of tap water is 2.71 L/day, whereas the average daily total water intake is 3.79 L (*66*).

Table 2. Ranking possible carcinogenic hazards with the use of the methodology of Ames et al. (2)*

Possible hazard (HERP %)	Carcinogenic exposure	Average daily carcinogen dose (70-kg adult)	Potency of carcinogen TD_{50} (mg/kg)	Comment†
	Man-made chemicals in foods/beverages			
0.02	Daminozide in treated apples and apple juice (1987)	20 μg	1.2	(1)
0.002	Daminozide in peanuts and peanut butter (1987)	1.9 μg	1.2	(1)
0.03	DBCP in treated carrots (preregulatory, 1976)	5.1 μg	0.24	(2)
0.003	DDT, DDD, and DDE in food (preregulatory, 1968-1969)	29.0 μg	13	(3)
0.0003	DDT, DDD, and DDE in food (postregulatory, (1980-1982)	2.3 μg	13	(3)
0.002	Dieldrin in food (preregulatory, 1968-1969)	1.5 μg	1.1	(4)
0.001	Dieldrin in food (postregulatory, 1980-1982)	1.1 μg	1.1	(4)
0.004	EDB in treated apples (preregulatory)	4.1 μg	1.5	(5)
0.0004	EDB in grain products (preregulatory, 1983)	0.42 μg	1.5	(5)
0.01	PCBs in food (preregulatory, 1971)	15 μg	1.7	(6)
0.0002	PCBs in food (postregulatory, 1980-1982)	0.2 μg	1.7	(6)
0.003	Sodium saccharin in diet soda (1977-1978)	4.9 ng	2,100	(7)
	Natural carcinogens in foods and beverages			
0.003	Aflatoxins in peanuts and peanut butter (1977)	5.8 ng	0.0026	(8)
<0.0001	Estragole in basil	<3.8 μg	52	(9)
1.6	Ethyl alcohol in beer (1981)	10.2 g	9,100	(10)
0.4	Ethyl alcohol in wine (1981)	2.7 g	9,100	(10)
1.3	Ethyl alcohol in hard liquor (1981)	8.1 g	9,100	(10)
0.01	Hydrazines in mushrooms (1977)	0.16 g	20,000	(11)
0.001	DMN in cured meat and bacon (1980)	0.12 μg	0.16	(12)
0.002	DEN in cured meat and bacon (1980)	0.034 μg	0.021	(12)
	Ambient air pollutants			
0.03	Benzene (Los Angeles, preregulatory, 1968)	1.0 mg	53	(13)
0.009	Benzene (Los Angeles, postregulatory, 1984)	0.32 mg	53	(13)
0.0005	Carbon tetrachloride (U.S. urban and surburban areas, 1973-1974)	48 μg	140	(14)
0.0004	Carbon tetrachloride (U.S. urban areas, 1980)	42 μg	140	(14)
0.0002	DDT (U.S. rural areas, preregulatory, 1972)	2.0 μg	13	(15)
0.00003	DDT (U.S. rural areas, postregulatory, 1974)	0.24 μg	13	(15)
0.004	EDB (U.S. urban areas, 1980-1981)	4.3 μg	1.5	(16)
1.8	Formaldehyde (Los Angeles, 1966)	1.9 mg	1.5	(17)
0.4	Formaldehyde (Los Angeles, 1979)	370 μg	1.5	(17)
0.002	PCBs (U.S. suburban areas, preregulatory, 1975)	2 μg	1.7	(18)
0.0001	PCBs (U.S. urban areas, postregulatory, 1979)	150 ng	1.7	(18)
0.003	Tetrachloroethylene (Bayonne, NJ, 1973)	220 μg	100	(19)
0.001	Tetrachloroethylene (Bayonne, NJ, 1983)	92 μg	100	(19)
0.001	Toxaphene (U.S. rural areas, 1972)	5.2 μg	5.8	(20)
	Indoor air pollutants			
0.005	Benzene (personal average, New Jersey, 1981)	173 μg	53	(21)
0.0002	Carbon tetrachloride (personal average, New Jersey, 1981)	16.2 μg	140	(22)
0.01	Chlordane (average in treated homes, 1976-1982)	20.5 μg	2.4	(23)
0.6	Formaldehyde in conventional homes (average of all reported U.S. data)	600 μg	1.5	(24)
2.1	Formaldehyde in mobile homes (U.S. average, 1984)	2.2 mg	1.5	(24)
0.02	Heptachlor (average in treated homes, 1982)	13.9 μg	1.2	(25)
0.001	Tetrachloroethylene (personal average, New Jersey, 1981)	80 μg	100	(26)
	Water pollutants			
0.0001	Chlordane (Kansas City drinking water, preregulatory, 1965-1967)	0.14 μg	2.4	(27)
0.003	Chloroform (average U.S. drinking water, 1976)	170 μg	90	(28)
0.01	DBCP (California, postregulatory, 1984)	2.0 μg	0.24	(29)
0.007	EDB (Florida, groundwater, 1983)	7.8 μg	1.5	(30)
0.03	Heptachlor (South Carolina rural drinking water, preregulatory, 1977)	24 μg	1.2	(31)
0.0003	PCBs (U.S. surface water, preregulatory, 1971-1974)	0.4 μg	1.7	(32)
0.0002	Tetrachloroethylene (New Jersey water supplies, 1985)	12 μg	100	(33)
0.00002	TCE (U.S. water supplies, 1985)	14 μg	940	(34)
0.0002	Vinylidine chloride (New Jersey water supplies, 1985)	4 μg	24	(35)

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Table 2. Continued

Possible hazard (HERP %)	Carcinogenic exposure	Average daily carcinogen dose (70-kg adult)	Potency of carcinogen TD_{50} (mg/kg)	Comment†
	Occupational exposures			
32.3	Benzene (rubber industry, preregulatory, 1942)	1.2 g	53	(36)
0.06	Benzene (rubber industry, postregulatory, 1980s)	2.4 mg	53	(36)
105.0	Formaldehyde (resin and paper manufacture, 1961)	110 mg	1.5	(37)
3.0	Formaldehyde (resin and plastic manufacture, 1980s)	3.2 mg	1.5	(37)
6.2	TCE (small factories, preregulatory, 1940s)	4.1 g	940	(38)
0.2	TCE (postregulatory, 1980s)	0.1 g	940	(38)

*The selection of chemicals and the estimates of exposure differ somewhat from those in Ames et al., as described in the text. To calculate average daily dose over an individual lifetime, we assumed: *a*) food consumption according to nationwide surveys; *b*) water consumption: 2 L/day; *c*) ambient air: inhalation of 20,000 L/day; *d*) indoor air: inhalation of 10,800 L/14-hr day; *e*) workplace air: inhalation of 9,600 L/day, 5 days/wk, 50 wk/yr, 40/70 yr (i.e., 3,768 L/day over an average lifetime) (*68*). For carcinogens listed as ambient and indoor air pollutants, the respective HERPs cannot be considered additive, since the 20,000 L/day may include both types of exposure. We also calculated exposure for a 70-kg male adult, although a 60-kg adult is more reasonable (*69*). When only a range of values was reported in the literature, their geometric mean was used as the average exposure. The HERP is derived by dividing the daily carcinogen dose by 70 kg to provide a milligram-per-kilogram value, which is then given as the percentage of the TD_{50} dose in the rodent (also in mg/kg).

†*See* appendix for comments.

Table 3. Comparison of possible carcinogenic hazards (HERPs) as estimated by Ames et al. and with the use of average exposure estimates*,†

Carcinogenic exposure	Ames et al. estimate: Average exposure	Ames et al. estimate: Worst-case exposure	Our estimate, average exposure
Man-made chemicals in foods and beverages			
DDE/DDT in food			
Preregulatory	—	—	0.003
Postregulatory	0.0003	—	0.0002
EDB in grains	0.0004	—	0.0004
PCBs in food			
Preregulatory	—	—	0.01
Postregulatory	0.0002	—	0.0002
Sodium saccharin in diet sodas	—	0.06	0.003
Natural carcinogens in foods and beverages			
Aflatoxins in peanuts and peanut butter	—	0.03	0.003
DMN in cured meat and bacon	—	0.003	0.001
DEN in cured meat and bacon	—	0.006	0.002
Estragole in basil	—	0.1	<0.0001
Ethyl alcohol in beer	—	2.8	1.6
Ethyl alcohol in wine	—	4.7	0.4
Hydrazines in mushrooms	—	0.1	0.01
Ambient air pollutants			
Formaldehyde in conventional home air	0.6	—	0.6
Formaldehyde in mobile home air	2.1	—	2.1
Water pollutants			
Chloroform in water	0.001	—	0.003
Tetrachloroethylene in water	—	0.0003	0.0002‡
TCE in water	—	0.004	0.00002§
Occupational exposures			
Formaldehyde in workplace air	5.8	—	3.0

*DMN = *N*-nitrosodimethylamine, DEN = *N*-nitrosodiethylamine, and TCE = trichloroethylene.
†*See* tables 1 and 2 for details on daily carcinogenic dose and TD_{50}.
‡Worst-case assumption: HERP % = 0.007.
§Worst-case assumption: HERP % = 0.1.

population, shows that the selected man-made or industrial pollutants generally are comparable in terms of HERP scale to naturally occurring carcinogens in the diet. Because of the limitations in the HERP approach, however, we stress that regulatory agencies would be unwise to base public health policies principally on comparisons such as these.

Finally, Ames et al. (*2*) asserted that nine of the 26 carcinogens listed in table 1 "are thought to be nongenotoxic" and are therefore likely to have nonlinear dose-response curves or a decreased risk at lower dose. This subject has been discussed frequently (*146-149*). The general consensus on the part of regulatory agencies and expert groups has been that such policy distinctions are premature because they are supported inadequately by scientific data (*19,63,147,150,151*).

There are few, if any, clear-cut promoters and initiators; rather, there is evidence that under different conditions the same carcinogen can operate as a complete carcinogen, an initiator, or a promoter (*147*). For example, TCDD has demonstrated the ability to act both as a complete carcinogen and a promoter (*152-155*). It is just as difficult to distinguish between genotoxic and nongenotoxic agents because in most cases short-term tests for genetic toxicity have generated a mixture of positive and negative results. This phenomenon has been observed with a variety of chemicals regarded up to this time as model "epigenetic, late stage" carcinogens: asbestos, the phorbol ester 12-*O*-tetradecanoylphorbol-13-acetate, diethylstilbestrol, and DDT. These compounds have induced a variety of genetic effects, either indirectly or directly, in experimental systems or in humans (*149*).

The nine so-called nongenotoxic carcinogens in table 1 illustrate the difficulty of making such categorical distinctions. Although in most instances the majority of short-term test results have been negative, each of the compounds (with the exception of clofibrate) has tested positive in at least one assay for each of several different genetic toxicity end points

(156).[6] For eight of the nine chemicals, although the evidence of genetic toxic effects is generally limited, it cannot be dismissed. Therefore, it is not possible to conclude definitively that these are nongenotoxic carcinogens that do not act at some stage and under some conditions, either directly or indirectly, by damaging the genetic material. Viewed in a larger context, the proposed distinction among carcinogens on the basis of presumed mechanism or stage at which they act is belied by the observation that control of late-stage carcinogens that may not be genotoxic may lead to the most rapid reduction in risk, as has been seen with postmenopausal estrogen therapy and cigarette smoking (158).

In summary, there is no question that both occupational and food carcinogens are real concerns. However, while the hazards of the workplace are relatively well characterized (68), there is clearly a need for more research on dietary carcinogens. At the same time, there is evidence from epidemiologic, experimental, and monitoring sources that the cumulative risks of environmental pollution are important. Despite its limitations, the HERP analysis for a selection of exposures prevalent in the U.S. environment tends to support this conclusion. Although it is not possible to estimate the magnitude of these risks with certainty, it is prudent to continue to reduce involuntary exposures to carcinogens. The dramatic decrease in estimated cancer risk following regulation of a number of industrial chemicals illustrates this point. Controlling exposures to carcinogens such as those listed in table 2 has important side benefits in that many carcinogens are mutagenic, teratogenic, reproductive, or neurological toxicants (36).

[6]As summarized by the IARC, chloroform has been positive in only one of many assays for gene mutation in bacteria and has been largely negative in other systems used. However, it has tested positive in lower eukaryotic systems (inducing differential toxic effects in DNA repair-deficient strains, gene conversion, and/or recombination and reverse mutation). Trichloroethylene has been positive in a number of assays. It has induced genetic toxic effects in bacteria (mutation), in yeast (gene conversion or recombination and mutation), in *Tradescantia* (mutation), in rodent cells (transformation), in human cells in vitro [unscheduled DNA synthesis (UDS) and sister chromatid exchanges (SCEs)], in animals in vitro (DNA damage), and in animal cells in vivo (mutation and micronuclei). Tetrachloroethylene, PCBs, and DDT have been largely negative in assays for genetic toxic effects; however, for tetrachloroethylene there have been positive results in yeast (recombination or gene conversion), in *Tradescantia* (mutation), and in animal cells (transformation and DNA damage). PCBs have induced DNA damage in animal cells in vitro and UDS in rat primary hepatocytes. DDT has been positive in insect systems (dominant lethal mutation and aneuploidy), animal cells in vitro (chromosome aberrations), and animal cells in vivo (chromosome aberrations and dominant lethal mutation). Ethyl alcohol has been studied extensively; a significant number of positive results were found. Evidence of genetic toxic effects includes gene conversion or recombination, mutation, and aneuploidy in lower eukaryotic systems; SCE, micronuclei, and chromosome aberrations in plant systems; SCE, chromosome aberrations, and aneuploidy in animal cells in vitro; SCE, chromosome aberrations, micronuclei, dominant lethal mutations, and aneuploidy in animal cells in vivo; and SCE and chromosome aberrations in human cells in vivo. Alcoholism is associated with increased incidence of chromosome aberrations (157). For phenobarbitol, the preponderance of results has been negative. However, there is evidence for the induction of gene mutation in bacteria and aneuploidy in yeast; gene mutation, SCE, and chromosome aberrations in rodent cells in vitro; cell transformation in rodent cells; as well as gene mutation and chromosome aberrations in human cells in vitro. Clofibrate has only been tested in two assays, both of which were negative. Finally, sodium saccharin has evidence of genetic toxic effects in lower eukaryotic systems (gene conversion or recombination and mutation), in insects (mutation), in animal and human cells in vitro (SCE and chromosome aberrations), and in animals in vivo (SCE and mutation).

References

1. Higginson J, Muir CS. The role of epidemiology in elucidating the importance of environmental factors in human cancer. Cancer Detect Prev 1976;1:79-105.
2. Ames BN, Magaw R, Gold LS. Ranking possible carcinogenic hazards. Science 1987;236:271-280.
3. Hiatt HH, Watson JD, Winsten JA, eds. Origins of human cancer. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977.
4. Mulvihill JJ. Genetic repertory of human neoplasia. In: Mulvihill JJ, Miller RW, Fraumeni JF Jr, eds. Genetics of human cancer. New York: Raven Press, 1977:137-143.
5. Miller DG. On the nature of susceptibility to cancer. Cancer 1980;46:1307-1318.
6. Day NE. Statistical considerations. In: Wald NJ, Doll R, eds. Interpretation of negative epidemiologic evidence of carcinogenicity. Lyon, France: IARC, 1985:13-27.
7. Wilkins JR, Reiches NA, Kruse CW. Organic chemical contaminants in drinking water and cancer. Am J Epidemiol 1979;110:420-448.
8. National Research Council. Drinking water and health, vol 3. Washington, DC: Natl Acad Press, 1980.
9. Gottlieb MS, Carr JK, Clarkson JR. Drinking water and cancer in Louisiana: a retrospective mortality study. Am J Epidemiol 1982;116:652-667.
10. Crump KS, Guess HA. Drinking water and cancer: review of recent epidemiological findings and assessment of risks. Annu Rev Public Health 1982;3:339-357.
11. Cantor KP, Hoover R, Hartge P, et al. Bladder cancer, drinking water source, and tap water consumption: a case-control study. JNCI 1987;79:1269-1279.
12. Maclure KM, MacMahon B. An epidemiologic perspective of environmental carcinogenesis. Epidemiol Rev 1980;2:19-48.
13. Cohen L. Diet and cancer. Sci Am 1987;257:42-48.
14. Decouflé P. Occupation. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: Saunders, 1982:318-335.
15. National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: Natl Acad Press, 1986.
16. Blot WJ. Clues to environmental determinants of cancer from its geographic patterns: In: Breslow NE, Whittemore AS, eds. Energy and health. Proceedings of a SIMS conference. Philadelphia: SIAM, 1979:151-167.
17. Nisbet ICT, Schneiderman MA, Karch NJ, et al. Review and evaluation of evidence for cancer associated with air pollution. Research Triangle Park: EPA Office of Air Quality Planning and Standards, 1984 [publication No. (EPA) 450/5-83-006R].
18. Karstadt M, Bobal R, Selikoff IJ. A survey of availability of epidemiologic data on humans exposed to animal carcinogens. In: Peto R, Schneiderman M, eds. Quantification of occupational cancer. Banbury report No. 9. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1981:223-242.
19. Office of Technology Assessment. Identifying and regulating carcinogens. Washington, DC: US Govt Print Off, 1987.
20. Council on Environmental Quality. Contamination of groundwater by toxic organic chemicals. Washington, DC: US Govt Print Off, 1981.
21. Office of Technology Assessment. Protecting the nation's groundwater from contamination. Washington, DC: US Govt Print Off, 1984 [publication No. (OTA)-0-233].
22. National Research Council. Drinking water and health, vol 1-6. Washington, DC: Natl Acad Press, 1977-1987.
23. Wallace LA, Pellizzari ED, Hartwell TD, et al. The TEAM study: personal exposures to toxic substances in air, drinking water, and breath of 400 residents of New Jersey, North Carolina and North Dakota. Environ Res 1987;43:290-307.
24. Harris RH, Page T, Reiches NA. Carcinogenic hazards of organic chemicals in drinking water. In: Hiatt HH, Watson JD, Winsten JA,

eds. Book A. Incidence of cancer in humans. Cold Spring Harbor, NY: Cold Spring Harbor Laboratory, 1977:309-330.
25. HUNT WF JR, FACRO RB, CURRAN TC, et al. Estimated cancer incidence rates for selected toxic air pollutants using ambient air pollution data. Research Triangle Park: EPA Office of Air and Radiation, 1984.
26. National Academy of Sciences. Regulating pesticides in food: the Delaney paradox. Washington, DC: Natl Acad Press, 1987.
27. MURPHY RS, KUTZ FW, STRASSMAN SC. Selected pesticide residues or metabolites in blood and urine specimens from a general population survey. Environ Health Perspect 1983;48:81-86.
28. Environmental Protection Agency. A cancer risk-specific dose estimate for 2,3,7,8-TCDD (draft). Washington DC: EPA, 1987.
29. COLE P. Cancer and occupation: status and needs of epidemiologic research. Cancer 1977;39:1788-1791.
30. BRIDBORD K, DECOUFLÉ P, FRAUMENI JF JR, et al. Estimates of the fraction of cancer in the United States related to occupational factors. National Cancer Inst., NIEHS and NIOSH, September 15, 1978 (reproduced in ref. *18*, pp. 701-726).
31. CEDERLOF R, DOLL R, FOWLER B, et al. Air pollution and cancer: risk assessment methodology and epidemiological evidence. Environ Health Perspect 1978;22:1-12.
32. DOLL R, PETO R, eds. The causes of cancer: quantitative estimates of avoidable risk of cancer in the United States today. London: Oxford Univ Press, 1981.
33. NICHOLSON WJ. Quantitative estimates of cancer in the workplace. Am J Ind Med 1984;5:341-342.
34. PIKE MC, GORDON RJ, HENDERSON BE, et al. Air pollution. In: Fraumeni JF Jr, ed. Persons at high risk of cancer. An approach to cancer etiology and control. New York: Academic Press, 1975:225-238.
35. DAVIS DL, LILIENFELD AD, GITTELSOHN A, et al. Increasing trends in some cancers in older Americans: fact or artifact. Toxicol Ind Health 1986;2:127-144.
36. TOMATIS L. Relation between mutagenesis, carcinogenesis, and teratogenesis: experience from the IARC monographs programme. Presented at the fourth international conference on environmental mutagens, Stockholm, June 24-28, 1985.
37. PERERA F. Quantitative risk assessment and cost benefit analysis for carcinogens at EPA: a critique. J Public Health Policy 1987;8:202-221.
38. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register, September 24, 1986;51:33992-34003.
39. CARTWRIGHT RA, ROGERS HJ, BARHAM-HALL D, et al. Role of *N*-acetyltransferase phenotypes in bladder carcinogenesis: a pharmacogenetic epidemiologic approach to bladder cancer. Lancet 1982;2:842-845.
40. HARRIS CC, TRUMP BF, GRAFSTROM R, et al. Differences in metabolism of chemical carcinogens in cultured human epithelial tissues and cells. J Cell Biochem 1982;18:285-294.
41. RITCHIE JC, IDLE JR. Population studies of polymorphism in drug oxidation and its relevance to carcinogenesis. In: Bartsch H, Armstrong, B, eds. Host factors in human carcinogenesis (IARC Sci Publ No. 39). Lyon, France: IARC, 1982:381-394.
42. OMENN GS. Advances in genetics and immunology: the importance of basic research to prevention of occupational diseases. Arch Environ Health 1984;39:173-182.
43. MARQUIS JK, SIEK GC. Sensitive populations and risk assessment in environmental policy-making. In: Saxena J, ed. Hazard assessment of chemicals, vol 6. Washington, DC: Hemisphere, 1988.
44. PERERA F. The significance of DNA and protein adducts in human biomonitoring studies. Mutat Res 1988;205:255-269.
45. HATTIS D, ERDREICH L, DIMAURO T. Human variability in parameters that are potentially related to susceptibility to carcinogenesis. I. Preliminary observations. Cambridge, MA: M.I.T. Center for Technology, Policy and Industrial Development, 1986 (report No. CTPID 86-4).
46. SETLOW RB. Variations in DNA repair among humans. In: Harris CC, Autrup H, eds. Human carcinogenesis. New York: Academic Press, 1983:231-254.
47. SELIKOFF IJ. Lung cancer and mesothelioma during prospective surveillance of 1249 asbestos insulation workers, 1963-1974. Ann NY Acad Sci 1976;271:448-456.
48. ARCHER VE. Enhancement of lung cancer by cigarette smoking in uranium and other miners. Carcinog Compr Surv 1985;8:23-37.
49. ZEISE L, WILSON R, CROUCH EAC. Dose-response relationships for carcinogens: a review. Environ Health Perspect 1987;73:259-308.
50. CROUCH E, WILSON R. Interspecies comparison of carcinogenic potency. J Toxicol Environ Health 1979;5:1095-1118.
51. California Department of Health Services. Health effects of benzene, report to the scientific review panel, part B. Sacramento, CA: CDHS, 1984.
52. ROWE JN, SPRINGER JA. Asbestos lung cancer risks: comparison of animal and human extrapolation. Risk Anal 1986;6:171-180.
53. ENTERLINE PE. A method for estimating lifetime cancer risks from limited epidemiologic data. Risk Anal 1987;7:91-96.
54. HERTZ-PICCIOTTO I, NEUTRA RR, COLLINS JF. Ethylene oxide and leukemia. JAMA 1987;257:2290.
55. HERTZ-PICCIOTTO, I, GRAVITZ N, NEUTRA RR. How do cancer risks predicted from animal bioassays compare with the epidemiologic evidence? The case of ethylene dibromide. Risk Anal. In press.
56. California Department of Health Services. Controlling risks from low dose exposure to proposition 65 carcinogens and reproductive toxins. DHS response to the proposed science advisory panel caveat. Sacramento, CA: CDHS, December 23, 1987.
57. PETO R, PIKE MC, BERNSTEIN L, et al. The TD_{50}: a proposed general convention for the numerical description of the carcinogenic potency of chemicals in chronic-exposure animal experiments. Environ Health Perspect 1984;58:1-8.
58. GOLD LS, SLONE TH, BACKMAN GM, et al. Second chronological supplement to the carcinogenic potency data base: standardized results of animal bioassays published through December 1984. Environ Health Perspect 1987;74:237-329.
59. GOLD LS, SAWYER CB, MAGAW R, et al. A carcinogenic potency data base of the standardized results of animal bioassays. Environ Health Perspect 1984;58:9-13.
60. GOLD LS, DE VECIANA M, BACKMAN GM, et al. Chronological supplement to the carcinogenic potency data base: standardized results of animal bioassays published through December 1982. Environ Health Perspect 1986;67:161-200.
61. HALLBERG GR, LIBRA RD, LONG KR, et al. Pesticides, groundwater and rural drinking water quality in Iowa. In: Pesticides and groundwater: a health concern for the Midwest. Navarre, MN: Public Freshwater Foundation, 1987:83-104.
62. National Toxicology Program. Fourth annual report on carcinogens: summary 1985. Research Triangle Park, NC: NTP, 1985 [publication No. (NTP)85-002].
63. International Agency for Research on Cancer. Overall evaluations of carcinogenicity: an updating of IARC monographs, vol 1-42. IARC Monogr Eval Carcinog Risk Chem Hum (suppl 7). Lyon, France: IARC, 1988.
64. SUGIMURA T, SATO S. Mutagens-carcinogens in foods. Cancer Res 1983;43(suppl):2415S-2421S.
65. National Research Council. Drinking water and health, vol 6. Washington, DC: Natl Acad Press, 1986.
66. ERSHOW AG, CANTOR KP. Population-based estimate of water intake. Fed Proc 1986;45:706.
67. International Agency for Research on Cancer. Some food additives, feed additives, and naturally occurring substances. IARC Monogr Eval Carcinog Risk Chem Hum 1983;31:47-61.
68. GOLD LS, BACKMAN GM, HOOPER NK, et al. Ranking the potential carcinogenic hazards to workers from exposures to chemicals that are tumorigenic in rodents. Environ Health Perspect 1987;76:211-219.
69. Environmental Protection Agency. Captan special review position document 2/3. Washington, DC: EPA, Office of Pesticides and Toxic Substances, 1985.
70. Environmental Protection Agency. Daminozide special review. Phase III market basket survey, 1987 [Uniroyal's submissions dated February 13 and 20, 1987; and April 13, 1987 (memo from L. Cheng to W. Waldrop, May 18, 1987)].
71. Environmental Protection Agency. Tolerance assessment system. Annualized chronic consumption data based upon the United States Department of Agriculture 1977 nationwide food consumption survey. Washington, DC: EPA, Office of Pesticide Programs, 1987.
72. NEWSOME WH, IVERSON F, PANOPIO LG, et al. Residues of dibromochloropropane in root crops grown in fumigated soil. J Agr Food Chem 1977;25:684-685.
73. DUGGAN RE, CORNELIUSSEN PE. Dietary intake of pesticide chemicals in the United States (III), June 1968-April 1970. Pest Monit J 1972;5:331-341.
74. Environmental Protection Agency. DDT: a review of scientific and economic aspects of the decision to ban its use as a pesticide. Washington, DC: EPA, 1975 [publication No. (EPA) 540/1-75-022].
75. GARTELL MJ, CRAUN JD, PODREBARAC DS, et al. Pesticides, selected elements and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 1986;69:146-161.
76. DUMAS T. Inorganic and organic bromide residues in foodstuffs fumigated with methyl bromide and ethylene dibromide at low temperatures. J Agr Food Chem 1983;21:433-436.
77. Environmental Protection Agency. Ethylene dibromide (EDB). Scien-

tific support and decision document for grain and-grain milling fumigation uses. Washington, DC: EPA, 1984.
78. JELINEK CF, CORNELIUSSEN PE. Levels of PCBs in the U.S. food supply. In: Proceedings of the national conference on polychlorinated biphenyls, Chicago, 1975. Washington, DC: EPA, 1976:163-165 [publication No. (EPA)560/6-75-004].
79. International Agency for Research on Cancer. Some non-nutritive sweetening agents. IARC Monogr Eval Carcinog Risk Chem Hum 1980:22:111-170.
80. PAO EM, FLEMING KH, GUENTHER PM. Foods commonly eaten by individuals: amount per day and per eating occasion. Washington, DC: US Dept of Agriculture, 1982.
81. National Research Council. Evaluation of cyclamates and carcinogenicity. Washington, DC: Natl Acad Press, 1985.
82. BUSBY WF, WOGAN GN. Aflatoxins. In: Searle CE, ed. Chemical carcinogens. Am Chem Soc Monogr 1984;182:945-1136.
83. STOLOFF L. Aflatoxin control: past and present. J Assoc Off Anal Chem 1980:6:1067-1073.
84. LEUNG AY. Encyclopedia of common natural ingredients. New York: Wiley, 1980.
85. TUYNS AJ. Alcohol. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention. Philadelphia: Saunders, 1982:293-303.
86. Distilled Spirits Council of the United States. Public revenues from alcohol beverages. Washington, DC: DISCUS, 1981. San Francisco: Wine Institute economic research report. CA: Wine Institute, 1983.
87. TOTH B, ERICKSON J. Cancer induction in mice by feeding of the uncooked cultivated mushroom of commerce *Agaricus bisporus*. Cancer Res 1986;46:4007-4011.
88. TOTH B. Mushroom hydrazines: occurrence, metabolism, carcinogenesis, and environmental implications. In: Miller EC, ed. Naturally occurring carcinogens, mutagens, and modulators of carcinogenesis. Tokyo: Japan Sci Soc 1979:57-65.
89. PREUSSMANN R. Occurrence and exposure to N-nitroso compounds and precursors. In: O'Neill IK, Von Borstel RC, Miller CT, et al, eds. *n*-Nitro compounds: occurrence, biological effects and relevance to human cancer. Lyon, France: IARC, 1984:3-15.
90. CHOI BCK. N-nitroso compounds and human cancer. Am J Epidemiol 1985;121:737-743.
91. SEN NP, SEAMAN S, MILES WF. Volatile nitrosamines in various cured meat products: effects of cooking and recent trends. J Agr Food Chem 1979;27:1354-1357.
92. SCANLAN RA. Formation and occurrence of nitrosamines in food. Cancer Res 1983;43:2435S-2440S.
93. International Agency for Research on Cancer. Some industrial chemicals and dyestuffs. IARC Monogr Eval Carcinog Risk Chem Hum 1982;29:93-148; 345-389.
94. LONNEMAN WA, BELLAR A, ALTSHULLER AP. Aromatic hydrocarbons in the atmosphere of the Los Angeles basin. Environ Sci Technol 1968;2:1017-1020.
95. National Academy of Science. Benzene in air. Washington, DC: Natl Acad Press, 1980.
96. HUNT WF JR, FAORO RB, FREAS W. Report on the interim data base for state and local air toxic volatile organic chemical measurements. Washington, DC: EPA, 1986 [publication No. (EPA) 450/4 86 012].
97. International Agency for Research on Cancer. Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum 1979;20:371-399.
98. LILLIAN D, SINGH HB, APPLEBY A, et al. Atmospheric fates of halogenated compounds. Environ Sci Technol, 1975;9:1042-1048.
99. LOVELOCK JE, MAGGS RJ, WADE RJ. Halogenated hydrocarbons in and over the Atlantic. Nature 1973;241:194-196.
100. HANST PL, SPILLER LL, WATTS DM, et al. Infrared measurement of fluorocarbons, carbon tetrachloride, carbonyl sulfide, and other atmospheric trace gases. J Air Pollut Control Assoc 1975;25:1120-1226.
101. SINGH HB, FOWLER DP, PEYTON TO. Atmospheric carbon tetrachloride: another man-made pollutant. Science 1976;192:1231-1234.
102. ARTHUR RD, CAIN JD, BARRENTINE BF. Atmospheric levels of pesticides in the Mississippi Delta. Bull Environ Contam Toxicol 1976;15:129-134.
103. STANLEY CW, BARNEY JE, HELTON MR, et al. Measurement of atmospheric levels of pesticides. Environ Sci Technol 1971;5:430-435.
104. SINGH HB, SALAS LJ, SMITH AJ, et al. Measurements of some potentially hazardous organic chemicals in urban environments. Atmos Environ 1981;15:601-612.
105. SINGH HB, SALAS LJ, STILES RE. Distribution of selected gaseous organic mutagens and suspect carcinogens in ambient air. Environ Sci Technol 1982:16:872-880.
106. PATTERSON RM, BORNSTEIN ML, GARSHICK E. Assessment of formaldehyde as a potential air pollution problem, vol 8. Bedford, MA: EPA, 1976.
107. KITCHENS RD, CASNER RE, EDWARDS GS, et al. Investigation of selected potential environmental contaminants: formaldehyde. Washington, DC: EPA [publication No. (EPA)560/2-76-009].
108. Versar Inc. Human exposure to formaldehyde. Draft report (contract No. 68-01-5791 for Office of Pesticides and Toxic Substances, Environmental Protection Agency, Springfield, VA), 1980.
109. CLEVELAND WS, GRAEDEL TE, KLEINER B. Urban formaldehyde: observed correlation with source emissions and photochemistry. Atmos Environ 1977;11:357-360.
110. KUTZ FW, YANG HSC. A note on polychlorinated biphenyls in air. In: Proceedings of the national conference on polychlorinated biphenyls, Chicago, 1975. Washington, DC: EPA, 1976:182 [publication No. (EPA)560/6-75-004].
111. EISENREICH SJ, LOONEY BB, THORNTON JD. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 1981;15:30-38.
112. EISENREICH SJ, LOONEY BB, HOLLOD GJ. PCBs in the Lake Superior atmosphere 1978-80. In: Mackay D, Paterson S, Eisenreich SJ, et al, eds. Physical behavior of PCBs in the Great Lakes. Ann Arbor, MI: Ann Arbor Sci, 1983:115-125.
113. International Agency for Research on Cancer. Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum 1979:20:491-514.
114. SINGH HB. Phosgene in the ambient air. Nature 1976;264:428-429.
115. LIVINGSTON JM, JONES CR. Living area contamination by chlordane used for termite treatment. Bull Environ Contam Toxicol 1981;27:406-411.
116. WRIGHT CG, LEIDY RB. Chlordane and heptachlor in the ambient air of houses treated for termites. Bull Environ Contam Toxicol 1985;28:617-623.
117. FENSKE RA, STERNBACH T. Indoor air levels of chlordane in residences in New Jersey. Bull Environ Contam Toxicol 1987;39:903-910.
118. LOUIS JB, KISSELBACH KC JR. Indoor air levels of chlordane and heptachlor following termiticide applications. Bull Environ Contam Toxicol 1987;39:911-918.
119. CONNOR TH, THEISS JC, HANNA HA, et al. Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol Lett 1985;25:33-40.
120. SCHAFER ML, PEELER JT, GARDNER WS, et al. Pesticides in drinking water: waters from the Mississippi and Missouri rivers. Environ Sci Technol 1969;12:1261-1269.
121. WILLIAMSON SJ. Epidemiological studies on cancer and organic compounds in U.S. drinking water. Sci Total Environ 1981;18:187-203.
122. WILLIAMS DT. Formation of trihalomethanes in drinking water. In: Fishbein L, O'Neill IK, eds. Environmental carcinogens: selected methods of analysis, vol 7 (IARC publications No. 68). Lyon, France: IARC, 1985:69-88.
123. Environmental Protection Agency. Tolerance assessment system. Annualized chronic consumption data based upon the United States Department of Agriculture 1977 nationwide food consumption survey. Washington, DC: EPA, Office of Pesticide Programs, 1987.
124. COHEN DB, BOWES GW. Water quality and pesticides: a California risk assessment program, vol I. Sacramento, CA: State Water Resources Control Board (Toxic Substances Control Program), 1984.
125. Environmental Protection Agency. Ethylene dibromide (EDB) position document 4. Washington, DC: EPA, Sept 27, 1983.
126. SANDHU SS, WARREN WJ, NELSON P. Pesticidal residue in rural potable water. J Am Water Works Assoc 1978;70:41-45.
127. DENNIS DS. Polychlorinated biphenyls in the surface waters and bottom sediments of the major drainage basins of the United States. In: Proceedings of the national conference on polychlorinated biphenyls, Chicago, 1976. Washington, DC: EPA, 1976:183-194 [publication No. (EPA)560/6-75-004].
128. New Jersey Department of Environmental Protection. Results of testing for hazardous contaminants in public water supplies under Assembly Bill A-280. Final report. Trenton: NJDEP, 1987.
129. International Agency for Research on Cancer. Some halogenated hydrocarbons. IARC Monogr Eval Carcinog Risk Chem Hum 1979:20:545-572.
130. American Water Works Association. Materials for research workshop on volatile organic chemicals. Denver: AWWA, 1972.
131. International Agency for Research on Cancer. Some monomers, plastics and synthetic elastomers, and acrolein. IARC Monogr Eval Carcinog Risk Chem Hum 1979;19:439-459.
132. California Department of Health Services. Organic chemical contam-

ination of large public water systems in California. Sacramento, CA: CDHS. 1986.
133. Environmental Protection Agency. Ambient water quality criteria for benzene. Washington, DC: EPA, 1980 [publication No. (EPA) 440/5-80/018].
134. RUNION HE, SCOTT LM. Benzene exposure in the United States 1978-1983: an overview. Am J Ind Med 1985;7:385-393.
135. National Institute for Occupational Safety and Health. Criteria for a recommended standard. Occupational exposure to formaldehyde. Washington, DC. US Govt Print Off, 1976 [DHEW publication No. (NIOSH) 77-125].
136. National Academy of Sciences. Formaldehyde: an assessment of its health effects. Prepared for the Consumer Products Safety Commission. Washington, DC: Natl Acad Sci Press, 1980.
137. SIEGEL DM, FRANKOS VH, SCHNEIDERMAN MA. Formaldehyde risk assessment for occupationally exposed workers. Regul Toxicol Pharmacol 183:3:355-371.
138. BERNSTEIN RS, STAYNER LT, ELLIOTT LJ, et al. Inhalation exposure to formaldehyde: an overview of its toxicology, epidemiology, monitoring and control. Am Ind Hyg Assoc J 1984;45:778-785.
139. Environmental Protection Agency. Technical document. Formaldehyde. Washington, DC: EPA, Office of Pesticides and Toxic Substances, November 16, 1981.
140. FLINN FB. Industrial exposures to chlorinated hydrocarbons. Am J Med 1946;1:388-394.
141. KLEINFELD M, TABERSHAW IR. Trichloroethylene toxicity. AMA Arch Ind Hyg 1954;10:134-141.
142. KIMBROUGH RD, MITCHELL FL, HOUK VN. Trichloroethylene: an update. J Toxicol Environ Health 1985;15:369-383.
143. SILBERGELD E. Risk assessment. Science 1987;237:1399.
144. BROWN HS, BISHOP DR, ROWAN CA. The role of skin absorption as a route of exposure for volatile organic compounds (VOCs) in drinking water. Am J Public Health 1984;74:479-484.
145. New York State Department of Health. A risk assessment for ethylene dibromide. Bureau of Toxic Substance Assessment, NYSDH, Feb 21, 1984.
146. WILLIAMS GM, WEISBURGER JH. Carcinogen risk assessment. Science 1983;221:6.
147. International Agency for Research on Cancer. Approaches to classifying chemical carcinogens according to mechanism of action. Lyon, France: IARC, 1983 (technical report No. 53/001).
148. WEINSTEIN IB. Letter to the editor. Science 1983;219:794-796.
149. PERERA F. The genotoxic/epigenetic distinction: relevance to cancer policy. Environ Res 1984;34:175-191.
150. Office of Science and Technology Policy. Chemical carcinogens: review of the science and its associated principles. Federal Register. March 14, 1985;50:10372-10442.
151. California Department of Health Services. Guidelines for chemical carcinogen risk assessments and their scientific rationale. Sacramento, CA: CDHS, 1985.
152. KOCIBA RJ, KEYES DG, BEYER JE. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol Appl Pharmacol 1978;46:279-303.
153. National Toxicology Program. Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin in Osborne Mendel rats and $B6C3F_1$ mice (gavage study). Research Triangle Park, NC: NTP, 1982 (technical report No. 209).
154. PITOT HC, GOLDSWORTHY T, CAMPBELL HA, et al. Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzo-p-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res 1980;40:3616-3620.
155. POLAND A, PALEN D, GLOVER E. Tumor production by TCDD in skin of HRS/J hairless mice. Nature 1982;300:271.
156. International Agency for Research on Cancer. Genetic and related effects: an update of selected IARC monographs, vol 1-42. IARC Monogr Eval Carcinog Risk Chem Hum (suppl 6). In press.
157. WATERS MD, STACK HF, BRADY AL, et al. Use of computerized data listings and activity profiles of genetic and related effects in the review of 195 compounds. Mutat Res 1988;205:295-312.
158. DAY NE, BROWN CC. Multistage models and primary prevention of cancer. JNCI 1980;64:977-989.